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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,661	02/28/2002	Masatoshi Chiba	P21749	5687

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
09/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/926,661	CHIBA, MASATOSHI	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *BPAI decision of 29 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-16 and 22-28* is/are pending in the application.

4a) Of the above claim(s) *22-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Board of Patent Appeals and Interferences has reversed the rejections of record.

Claims 1, 3, 4, 6 – 16, and 22 - 28 are pending.

Election/Restrictions

2. Claims 22 – 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 28 July 2005.

3. The requirement for an election of species with respect to stabilizing agents as set forth in the office action mailed 28 June 2005 is hereby vacated. Claims 1, 3 – 4, and 6 – 16 are under examination over their full scope.

Priority

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

New Rejections

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, and 6 – 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka (WO 97/02832, published 30 January 1997, of record) in view of Yamahira (U.S. Patent 4,244,943, issued 13 January 1981).

Note that Tanaka U.S. Patent Application Publication 2001/0051604 is the published version of the national stage entry of the PCT application that was published as WO 97/02832). Since 35 USC § 372(b)(3) requires that the application be submitted in English upon entry to the national stage, the '604 publication is a proper translation of the earlier Japanese document. The page and paragraph numbers cited herein are from the '604 publication but the same information was disclosed in Japanese in the earlier WIPO publication.

Tanaka teaches lyophilized compositions comprising hepatocyte growth factor (also known as HGF), a stabilizer, sodium chloride, buffer, and a surface active agent. See for example Tanaka paragraphs [0001] and [0007] – [0008]. This teaching is on point to instant claims 1 and 3, drawn to lyophilized compositions comprising HGF, a stabilizing agent, sodium chloride, and a buffering agent. Tanaka teaches that phosphate, which is a phophoric acid salt as recited in claim 7, is suitable as a buffering agent; see for example paragraph [0018] and paragraph [0028]. Tanaka explicitly states that the osmotic pressure ratio should be maintained so that the reconstituted HGF is suitable for injection (paragraph [0020]), which is on point to claims 8 – 9. Tanaka teaches that selection of pH 5.0 to 6.0, which is within the ranges recited in claims 10 – 11, is particularly desired as it leads to increased solubility; see paragraph [0018]. The teachings of Tanaka paragraph [0008] are also on point to instant claim 12,

drawn to a lyophilized preparation further comprising a surface active agent. Tanaka teaches that polysorbate 80 is a particularly preferred surface active agent (see paragraph [0019]), and this is well-known to be a polyoxyethylene ether surface active agent as encompassed by claims 12 - 13 and recited in claim 14. See instant specification, paragraph spanning pp. 9 – 10, which recognizes that polysorbate 80 is a member of this family of surface active agents. Tanaka indicates that vials, as recited in claim 15, can be used to prepare the lyophilized preparation; see for example paragraphs [0029] and [0031]. According to Tanaka, the stabilizing agent can include amino acids in general, and specifically names two examples (glycine and alanine) as suitable stabilizing agents. However Tanaka does not explicitly teach inclusion of arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid as the stabilizing agent, as recited in claims 1 and 3.

Yamahira teaches that addition of polar amino acids to solutions comprising protein prior to their lyophilization is sufficient to increase their stability following lyophilization. See for example column 1, lines 26 – 30 and column 1, line 64 – column 2, line 3. Yamahira specifically recites arginine, glutamic acid, and histidine as among the most preferred stabilizing amino acids; see column 2, lines 24 - 29. Each of these amino acids is recited in independent claims 1 and 3, as well as dependent claim 4. Arginine and histidine, taught by Yamahira to have superior ability to stabilize lyophilized protein solutions, are also recited in claim 6. However, Yamahira teaches that many of the amino acids listed in claims 1 and 3, including arginine, lysine, histidine, glutamine (called Glu(NH2) by Yamahira), glutamic acid, and aspartic acid, are suitable as stabilizing agents; see column 1, line 64 – column 2, line 3. Yamahira provides the results of an experiment which show that addition of arginine and histidine increase the residual potency of the active ingredient following lyophilization and a month of storage at 50 °C; see column 2, line 60 – column 3, line 35. However, while Yamahira teaches lyophilized preparations comprising a protein and the specific amino acids as stabilizing agents, the reference does not teach a preparation comprising HGF, as required by independent claims 1 and 3.

It would have been obvious to one of ordinary skill in the art to modify the invention of Tanaka by selecting any of the polar amino acids taught by Yamahira as the stabilizing agents, with a reasonable expectation of success. The motivation to do so would be to choose an amino acid known to be effective in stabilizing lyophilized preparations. Tanaka teaches that amino acids in general are suitable as stabilizing agents, and Yamahira guides the artisan to selection of the polar amino acids in general, and arginine and histidine in particular, as the patent shows that they are superior in stabilizing the protein following lyophilization. It would have been reasonable to expect success since both references are drawn to the same problem, namely how to stabilize a protein following lyophilization. See Tanaka paragraph [0004], where the reference teaches that HGF is "not so stable in freezing" and paragraph [0006] where the reference teaches that "... it is an object of the invention to present a stable preparation which can store for a long period"; see also paragraph [0008] which specifically directs the artisan to include a stabilizing agent. Yamahira provides the artisan of ordinary skill with guidance to select histidine and arginine in particular, as these are shown to be advantageous in that they have superior ability to stabilize the protein contained in the lyophilized preparation. While independent claims 1 and 3 recite that the stabilizing agent is "for preventing formation of an aggregate", this is an intended use of the stabilizing agent and need not necessarily be given patentable weight and is not construed as limiting. Since the reference by Yamahira specifically guides the artisan of ordinary skill to select at least one of the amino acids recited in the claims, the prior art references taken together render the claims obvious.

Claim 1 recites the limitation “which is prepared from an aqueous solution containing the hepatocyte growth factor at a concentration of lower than 5 mg/ml.” Claim 3 also recites this language, and additionally recites that the preparation is “capable of preparing an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/ml by redissolution.” It is noted that Tanaka provides several examples of lyophilized preparations of HGF prepared from solutions of 20 mg/ml HGF (see for example paragraphs [0025], [0029], and [0031]), as well as an example where HGF was at 10 mg/ml (paragraph [0032]). Tanaka does not explicitly

teach that the lyophilized preparation is to be prepared from an aqueous solution containing the HGF at 5 mg/ml or less. However, this is a product-by-process limitation which does not receive patentable weight in the absence of evidence that this limitation distinguishes the claimed product over that rendered obvious by the prior art; see MPEP § 2113. Additionally, the concentration of the solution could easily be optimized by varying the amount of solvent, and it is within the skill of the artisan to do so. Changes in concentration or dosage are generally not considered to be patentable; see MPEP § 2144.05(II). Thus even if the product-by-process limitation as to the concentration of HGF in the aqueous solution were to be given patentable weight, the adjustment of such concentration would generally be considered to be obvious, so this language which appears in claims 1 and 3 does not distinguish the claimed product from the prior art.

With respect to the limitation "capable of preparing an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/ml by redissolution" recited in claim 3, this refers to the concentration of HGF once the product is redissolved, which is an inherent property. Once the lyophilized product is reconstituted with the same volume of distilled water that was present prior to lyophilization, it will necessarily have the same concentration of components as existed prior to lyophilization. Thus this limitation recited in claim 3 is provided for. Additionally it is noted that Tanaka teaches that it is within the skill of the artisan to adjust the concentration; see paragraph [0021] final sentence.

Claim 16 is included in this rejection, note the claim does not specify a particular amount of the stabilizing agent that must be present. Claim 16 is drawn to an amount of the stabilizing agent sufficient to prevent HGF aggregate formation during lyophilization and/or storage after lyophilization. The examiner cannot determine if the amount used by Yamahira is sufficient to achieve the claimed property, prevention of aggregate formation. Nevertheless it is proper to include this claim in the rejection, since the prior art renders obvious the composition of claim 1. As claim 16 recites a property that appears to be inherent, and the prior art references render obvious the claimed

composition, the property is presumed to be provided for absent evidence to the contrary; see MPEP § 2112.01.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./
Patent Examiner, Art Unit 1649
September 15, 2008

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649

/Robert A. Wax/
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A Technology Center Director has approved reopening prosecution after decision by the Board of Patent Appeals and Interferences by signing below:

/JOHN L. LEGUYADER/
Director, Technology Center 1600